

NEW ZEALAND DATA SHEET

FIBALIP

Bezafibrate 200 mg tablet



Presentation

200mg Tablet: 10mm, biconvex, white film coated tablet, debossed "BZ" over "200" on one side and "G" on the other.

Uses

Actions

Bezafibrate lowers elevated blood lipids (triglycerides and cholesterol). Elevated VLDL and LDL are reduced by treatment with bezafibrate, whilst HDL-levels are increased. The activity of triglyceride lipases (lipoprotein lipase and hepatic lipoprotein lipase) involved in the catabolism of triglyceride-rich lipoproteins is increased by bezafibrate. In the course of the intensified degradation of triglyceride-rich lipoproteins (chylomicrons, VLDL) precursors for the formation of HDL are formed which explains an increase in HDL. Furthermore, cholesterol biosynthesis is reduced by bezafibrate, which is accompanied by a stimulation of the LDL-receptor-mediated lipoprotein catabolism.

Elevated fibrinogen appears to be an important risk-factor, alongside the lipids, smoking and hypertension, in the development of atheroma. Fibrinogen plays an important role in viscosity, and therefore blood flow, and also appears to play an important role in thrombus development and lysability.

Bezafibrate exerts an effect on thrombogenic factors. A significant decrease in elevated plasma fibrinogen levels can be achieved. This may lead, amongst other things, to a reduction in both blood and plasma viscosity. Inhibition of platelet aggregation has also been observed.

A reduction in blood glucose concentration due to an increase in glucose tolerance has been reported in diabetic patients. In the same patients, the concentration of fasting and postprandial free fatty acids was reduced by bezafibrate.

Pharmacokinetics

Absorption and Distribution

Bezafibrate is rapidly and almost completely absorbed from the standard film-coated tablet formulation. A peak plasma level of about 8mg/L is reached after 1-2 hours following a single 200mg dose in healthy volunteers.

94 – 96% of bezafibrate is bound to protein in human serum, and the apparent volume of distribution is about 17 litres.

Metabolism and Elimination

Elimination is rapid, with excretion almost exclusively renal. 95% of the activity of the ¹⁴C-labelled medicine is recovered in the urine and 3% in the faeces within 48 hours. 50% of the applied dose is recovered in the urine as the unchanged medicine and 20% in the form of glucuronides. The rate of renal clearance ranges from 3.4 to 6.0 L/hour. The elimination half-life of bezafibrate is 1-2 hours.

The elimination of bezafibrate is reduced in patients with impaired renal function and dosage adjustments are necessary to prevent accumulation and toxic effects.

There is a correlation between creatinine clearance and the elimination half-life of bezafibrate; with decreasing clearance the elimination half-life is increasing.

Pharmacokinetic investigations in the elderly suggest that elimination may be delayed in cases of impaired liver function. Liver disease (except fatty liver) is a contraindication.

Dialysis Behaviour

Bezafibrate cannot be dialysed (cuprophane filter).

Bioavailability

Bezafibrate is almost completely absorbed after oral administration.

Pharmacokinetics in Special Populations

In elderly patients, there is a physiological reduction of the renal function with age. Bezafibrate dosage should be adjusted based on the serum creatinine and creatinine clearance values as indicated in the table in the Dosage and Administration section.

Due to its high protein binding, bezafibrate cannot be dialysed (cuprophane filter). In all patients undergoing dialysis, the use of bezafibrate is contraindicated.

Indications

Bezafibrate is indicated for use in primary hyperlipidaemia of Type IIa, IIb, III, IV and V (Fredrickson Classification) corresponding to groups I, II and III of the European Atherosclerosis Society guidelines – when diet alone or improvements in lifestyle such as increased exercise or weight reduction do not lead to an adequate response.

Bezafibrate tablet is also indicated for secondary hyperlipidaemia e.g. severe hypertriglyceridaemias, when sufficient improvement does not occur after correction of the underlying disorder e.g. diabetes mellitus.

Dosage and Administration

Adults

The standard dosage for Fibalip 200 mg tablets is one tablet (200 mg) three times daily. In cases of good therapeutic response, especially in hypertriglyceridaemia, the dosage can be reduced to one 200mg tablet twice daily. For patients with a history of gastric sensitivity, the dosage may be gradually increased to the maintenance level.

Dosage In Renal Insufficiency

The dosage in patients with impaired renal function or dialysis must be adjusted according to serum creatinine levels or creatinine clearance.

Serum Creatinine	Creatinine Clearance	Dosage (200mg tablets)
Up to 1.5 mg/100ml Up to 135 µmol/l	Over 60 ml/min	3 tablets/day (1 tablet 3 times daily)
1.6 – 2.5 mg/100ml 136 – 225 µmol/l	60 – 40 ml/min	2 tablets/day (1 tablet twice daily)
2.6 – 6 mg/100ml 226 – 530 µmol/l	40 – 15 ml/min	1 tablet every 1 or 2 days
Over 6 mg/100ml Over 530 µmol/l Or dialysis patients	Less than 15 ml/min	Contraindicated

It should be taken into account that creatinine clearance (CL_{Cr}) is a more reliable parameter than serum creatinine (C_{Cr}) especially in the elderly. The creatinine clearance can be estimated using the following equation (Cockcroft and Gault equation) which is applicable to adults only:

$$\text{Men: } CL_{Cr} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)}}{72 \times C_{Cr} \text{ (mg/dl)}} \text{ ml/min}$$

For women, the value should be reduced to 85% of that estimated by this equation.

In dialysis patients, the use of bezafibrate is contraindicated. Bezafibrate dosage should be carefully adjusted based on the renal function and a careful evaluation of the benefit/risk ratio. To avoid overdosage (and thus e.g. rhabdomyolysis) regular measurement of bezafibrate plasma concentrations are advisable.

Duration of treatment

Treatment with bezafibrate is usually a long-term therapy.

Method of administration

Tablets should be swallowed whole with sufficient fluid, with or after meals.

Elderly

In elderly patients, there is a physiological reduction of the renal function with increasing age. Bezafibrate dosage should be adjusted according to the serum creatinine and creatinine clearance values as indicated in the above table.

Children

Indications for the use of bezafibrate in children must be particularly carefully considered. A definite dosage recommendation cannot be given.

Contraindications

Bezafibrate must not be used in:

- liver disease (with the exception of fatty liver which is a frequent accompaniment to hypertriglyceridaemia)
- gall bladder diseases with or without cholelithiasis (as a possible liver involvement cannot be excluded)
- hypersensitivity to the bezafibrate, to any component of the product or to other fibrates
- patients with severe renal impairment presenting serum creatinine levels more than 6 mg / 100 mL (> 530 micromol/l) or creatinine clearance less than 15ml/min and all patients undergoing dialysis
- during pregnancy and lactation (see Pregnancy and lactation period)
- known photoallergic or phototoxic reactions to fibrates
- combination therapy of bezafibrate with HMG-CoA reductase inhibitors in patients with predisposing factors for myopathy e.g. pre-existing renal impairment, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance
- in elderly patients, as the creatinine clearance after 70 years of age is normally lower than 60 ml/min.

Warnings and Precautions

Compliance with diet and other measures, which improve lipid disorders such as physical activity, weight loss and adequate treatment of other metabolic disorders (e.g. diabetes, gout) is of utmost importance.

The patient's response to therapy should be monitored at regular intervals, and treatment should be terminated, if an adequate response has not been achieved with 3 to 4 months.

Indications for the use of bezafibrate in children must be particularly carefully considered. A definite dosage recommendation for children cannot be given.

Since oestrogens may lead to a rise in lipid levels, the prescribing of bezafibrate in patients taking oestrogens or oestrogen-containing contraceptives must be critically considered on an individual basis.

In patients with hypoalbuminaemia, e.g. nephrotic syndrome, and in patients with impaired renal function, the dosage of bezafibrate must be reduced and renal function should be monitored regularly. In patients with existing-renal impairment, acute renal failure may develop if dosage recommendations according to the presenting serum creatinine or creatinine clearance are not strictly followed.

Muscular weakness, myalgia and muscle cramps, often accompanied by a considerable increase in creatine kinase (CK) may occur. In isolated cases, severe muscular damage (rhabdomyolysis) has been observed. In most cases, this syndrome resulted from inappropriate usage of bezafibrate, most frequently in the presence of impaired renal function.

Due to the risk of rhabdomyolysis, bezafibrate should only be administered together with HMG CoA reductase inhibitors in exceptional cases when strictly indicated. Patients receiving this combination therapy must be informed carefully of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the first signs of myopathy. This combination therapy must not be used in patients with predisposing factors for myopathy (impaired renal function, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance).

Bezafibrate alters the composition of bile. There have been isolated reports of the development of gallstones. It is not certain whether the occurrence of gallstones is increased as a result of long-term treatment with bezafibrate, as has been observed with other medicines with a similar mechanism of action, or whether pre-existing gallstones increase in size in the course of bezafibrate therapy.

Since cholelithiasis as a possible side effect of bezafibrate therapy cannot be excluded, appropriate diagnostic procedures should be performed if cholelithiasis-related signs and symptoms should occur (use Adverse Effects).

When bezafibrate is given in combination with anion exchange resins (e.g. cholestyramine), the two medicines should be taken at least two hours apart.

Use in Pregnancy and Lactation

Due to lack of adequate experience, bezafibrate is contraindicated during pregnancy and lactation (see Contraindications).

Adverse Effects

The overall safety profile of bezafibrate is based on a combination of clinical data and post-marketing experience.

A total of 3,581 patients were enrolled into 48 clinical studies. Side-effects observed during the clinical development and subsequent use in clinical practice consisted mainly of symptoms of gastro-intestinal disturbances which were usually transient and rarely led to discontinuation of bezafibrate. Myopathy (rhabdomyolysis) was mostly observed when dose reduction was not implemented in patients with renal impairment. None of the side-effects could be considered to affect long-term safety, as they usually occurred within the first few months of therapy and were either transient or disappeared upon withdrawal of bezafibrate.

The frequency of adverse drug reactions (ADRs) according to MedDRA System Organ Class is displayed in the table below:

Frequency of reporting:	Common	>1/100 and <1/10
	Uncommon	≥1/1,000 and <1/100
	Rare	>1/10,000 and <1/1000
	Very rare	<1/10,000

**MedDRA System Organ Class
Frequency: Adverse Events**

Blood and Lymphatic System

Very rare: Pancytopenia
Thrombocytopenia

Immune System

Uncommon: Hypersensitivity reactions including anaphylactic reactions

Metabolism and Nutrition System

Common: Decreased appetite

Nervous System

Uncommon: Dizziness
Headache

Rare: Neuropathy peripheral
Paraesthesia

Gastro-intestinal Disorders

Common: Gastrointestinal disorder

Uncommon: Abdominal distension
Abdominal pain
Constipation
Diarrhoea
Dyspepsia
Nausea

Rare: Pancreatitis

Hepatobiliary Disorders

Uncommon: Cholestasis

Very rare: Cholelithiasis (See Special Warnings and Special Precautions for Use)

Skin and Appendages Disorders

Uncommon: Pruritus
Urticaria
Photosensitivity reaction
Alopecia
Rash

Very rare: Thrombocytopenic purpura
Erythema multiforme
Stevens-Johnson syndrome
Toxic epidermal necrolysis

Musculoskeletal and Connective Tissue Disorders

Uncommon: Muscular weakness
Myalgia
Muscle cramp

Very rare: Rhabdomyolysis

Renal and Urinary Disorders

Uncommon: Acute renal failure

Reproductive System and Breast Disorders	
<i>Uncommon:</i>	Erectile dysfunction NOS
Respiratory, thoracic and mediastinal disorders	
<i>Very rare:</i>	Interstitial lung disease
Psychiatric disorders:	
<i>Rare:</i>	Depression, insomnia, memory loss
Investigations	
<i>Uncommon:</i>	Increased blood creatinine phosphokinase Blood creatinine increased Blood alkaline phosphatase increased
<i>Very rare:</i>	Haemoglobin decreased Platelet increased White blood cell count decreased Gamma-glutamyl transferase increased Transaminase increased

Laboratory abnormalities

The following laboratory abnormalities have been observed during clinical trials and also reported during post-marketing period:

- Increased blood creatinine phosphokinase (uncommon)
- Increased platelets (uncommon)
- Decreased haemoglobin (uncommon)
- Decreased haematocrit (uncommon)
- Decreased white blood cells (uncommon)
- Increased transaminase (uncommon)
- Decreased alkaline phosphatase (uncommon)
- Decreased gamma-glutamyl transferase (uncommon) and in parallel alkaline phosphatase could be used as an indicator of patient compliance.

Interactions

When bezafibrate is used at the same time as other medicines or substances the following interactions must be taken into account:

Bezafibrate may enhance the action of anticoagulants of the coumarin type. For this reason, the dose of anti-coagulant should be reduced by 30 - 50% at the start of treatment with bezafibrate and then titrated according to the blood clotting parameters.

The action of sulphonylureas and insulin may be enhanced by bezafibrate. This may be due to an improved glucose utilisation with simultaneous reduction in insulin requirement.

In isolated cases, a pronounced though reversible, impairment of renal function (accompanied by a corresponding increases in the serum creatinine level) has been reported in organ transplant patients receiving immuno-suppressant therapy and concomitant bezafibrate. Accordingly, renal function should be closely monitored in these patients and, in the event of relevant significant changes in laboratory parameters, bezafibrate should, if necessary, be discontinued.

When bezafibrate is used concurrently with anion exchange resins (e.g. cholestyramine), an interval of at least two hours should be maintained between the two medicines, since the absorption of bezafibrate is impaired.

Perhexiline hydrogen maleate or MAO-inhibitors (with hepato-toxic potential) must not be administered together with bezafibrate.

Interaction between fibrates and HMG-CoA reductase inhibitors (statins) may vary in nature and intensity depending on the combination of the administered medicines. A pharmacodynamic interaction between these two classes of medicines may in some cases, also contribute to an increased risk of myopathy (rhabdomyolysis).

Overdosage

As the specific clinical picture of intoxication is unknown, symptomatic therapy should be given as necessary. There is no specific antidote.

In cases of rhabdomyolysis (mostly in patients with impaired renal function), administration of bezafibrate must be stopped immediately and renal function must be carefully monitored.

Pharmaceutical Precautions

Store in a cool, dry place below 30°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Tablets 200mg: Bottles and Blister Packs of 90's.

Not all packaging presentation may be marketed.

Further Information

Since the first Consensus Conference of the European Atherosclerosis Society (held in Naples in June 1986), the proposed limits for disorders of lipid metabolism which are intended to be used as guidelines for diagnostic evaluation and corresponding therapeutic procedures have been increasingly applied. Accordingly, cholesterol and triglyceride values of 200mg/100ml (5.2mmol/l) and above in adults require medical attention.

In patients with elevated cholesterol and/or triglyceride values the overall risk of coronary heart disease should be estimated, taking into account the family history, HDL-cholesterol values below 35mg/100ml (0.9mmol/l), elevated fibrinogen levels, smoking habits, blood pressure, diabetes mellitus, male sex, overweight, lack of exercise and young age.

Ingredients

Each Fibalip tablet contains 200 mg of bezafibrate.

Each Fibalip tablet also contains microcrystalline cellulose, povidone, maize starch, purified talc, colloidal silicon dioxide, sodium starch glycollate, magnesium stearate and the contents of the film coat (hypromellose, titanium dioxide, lactose and polyethylene glycol).

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